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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,061	03/05/2002	Francis Y.F. Lee	LD0268 NP	6706

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 12/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,061	LEE, FRANCIS Y.F.	
	Examiner	Art Unit	
	Yong S. Chong	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-111 and 113-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-111 and 113-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/31/05, 11/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 10/31/2005. Claims 1-100, 112 have been cancelled. Claims 101-104, 111, 117, 126-127 have been amended. Claims 101-111, 113-130 are pending and are examined herein.

Response to Arguments

With regard to the 35 USC 102(e) rejection, applicant's arguments have been fully considered and found persuasive. The said rejection has been withdrawn.

With regard to the 35 USC 103(a) and obviousness-type double patenting rejections, applicant's arguments have also been fully considered but found not persuasive. The 103(a) rejections are maintained for reasons of record.

Firstly, applicant argues that there is no motivation to combine the references. Applicant is reminded of the motivation stated in the last Office Action referring to capecitabine being much safer and more effective than 5-FU, for treating cancers or various types of tumors (Miwa et al., abstract).

Secondly, applicant argues that there is no expectation of efficacy or synergism in the combination of capecitabine and ixabepilone. The reasons stated by applicant refer to the preclinical work done that suggests ixabepilone does not upregulate dThdPase levels.

Examiner argues that applicant's arguments are not commensurate with the scope of the claims. There is no limitation in the claims drawn to the upregulation of

dThdPase levels. Furthermore, this limitation cannot be found in any of the prior art references. In fact, applicant's arguments are not directed to the motivation used in the 103(a) rejection in any way. Again, the motivation to combine the references is because capecitabine is taught as being much safer and more effective than 5-FU, for treating cancers or various types of tumors.

Furthermore, it is obvious to combine capecitabine with ixabepilone since they are both taught for the same purpose.

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

The declaration under 37 CFR 1.132 filed 10/31/2005 is insufficient to overcome the rejection of claims 102-104, 112, 117-125 based upon Danishefsky et al. in view of Miwa et al. as set forth in the last Office action because: Applicant's arguments and data are not commensurate in scope of the claims as described above. Particularly, the data presented in the Declaration is based on colon carcinoma. The claims are directed to treating various cancers.

The claims must be commensurate in scope with any evidence of unexpected results. See MPEP 716.02 (d). Further, a DECLARATION UNDER 37 CFR 1.132 must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case of obviousness. See MPEP 716.02 (e).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 102-104, 112, and 117-125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danishefsky et al. (US 6867305) in view of Miwa et al. European Journal of Cancer (1998), 3448), 1274-1281, of record).

Danishefsky et al. discloses that administering a pharmaceutical composition comprising the instant particular compound (see the structure of the compound at col.108 lines 29-45) also known as C-15-Aza-EpoB (see Figure 33), azaepothilone b or ixabepilone to a mammal, is useful in methods of treating one or more of cancers such as cancerous solid tumors, refractory tumors, metastatic breast cancer, lung cancer, prostate cancer, and pancreatic cancer and methods for the treatment of cancer which has developed a muti-drug resistance (MDR) (see abstract, col. 59 lines 27-44).

In particular, the compounds of Danishefsky et al. such as the instant compound have been found effective not only reversing muti-drug resistance (MDR) in cancer cells both in vitro or in vivo, e.g., resistant to taxane treatment (paclitaxel or Taxol), but also more cytotoxic towards MDR cells than normal cells and as synergistic agents, which are more active in combination with other cytotoxic agents or anticancer agents than the individual drugs alone (see col.30 lines 15-32; col.59 line 45-59). Those other cytotoxic agents or anticancer agents such as 5-fluorouracil (5-FU) are used in

combination with the instant compounds (see col.59 line 60 to col.60 line 7).

The combination compositions of the instant compound and the other cancer drug can be administered substantially and simultaneously (concurrently) to humans or animals orally (see col.59 line 45-59., col. 57 lines 8-10) in various dosage forms (col.56-57).

Note that Danishefsky et al. discloses that the effective amount of the instant compound to be administered is in the range of about 0.01 ma to 50 mg/kg/day or 1 mg to 25 mg/kg/day (see col.57 lines 20-24), which are same or overlapping with the effective amounts, indicated in Applicant's specification (see page 39-41 of the specification).

Danishefsky et al. does not expressly disclose the employment of capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer.

Miwa et al. discloses that capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), which is finally converted to 5-fluorouracil (5-FU) by dThdpase in tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors. See abstract and the entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ capecitabine in combination with the instant particular

compound in a pharmaceutical composition and a method for treating cancer, since, first, 5-fluorouracil is known to be useful in combination with the instant particular compound in a pharmaceutical composition for methods for treating cancer effectively and synergistically, according to Danishefsky et al.

Second, capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), is known to be much safer and more effective than 5-FU and finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors.

Therefore, one of ordinary skill in the ad would have reasonably expected that combining capecitabine in combination with the instant particular compound in a pharmaceutical composition for methods for treating cancer, would have been much safer and even more effective than the combination of 5-FU and the instant compound in treating the same.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 101-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. WO 99/02514, of record) in view of The Merck Index, (12th ED), 1996, and Miwa et al. European Journal of Cancer (1998), 3448), 1274-1281 essentially for same reasons of record stated in the Office Action dated November 17, 2004.

Vite et al. discloses that the instant particular compound (see Example 3 at page 48) is useful in treating various types of cancers or tumors including the cancers recited in the instant claims 105-110 (see page 8-10). More important, Vite et al. discloses that the instant compound is useful in combination with known anti-cancer and cytotoxic

agents for cancer treatment. See page 10.

The prior art does not expressly disclose the employment of the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer.

The Merck Index teaches that fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy, i.e., combing with other anti-cancer agents as cancer chemotherapy drug regimens (see MISC-10).

Miwa et al. discloses that capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), which is finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors. See abstract and the entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer.

One having ordinary skill in the ad at the time the invention was made would have been motivated to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer, since the instant adicular compound is known to be useful in treating various types of cancers or tumors including the cancers herein and also useful in combination with known anti-cancer and

cytotoxic agents for cancer treatment according to Vite et al.

Moreover, fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy according to The Merck Index. Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), is known to be finally conrteded to 5-fluorouracil (5-FU) by dThdPase in tumors, and should be much safer and more effective than 5-FU, for treating cancers or various types of tumors according to Miwa et al.

Therefore, one of ordinary skill in the art would have reasonably expected that combining the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine and the instant compound, both known useful for the same purpose, i.e., treating cancers, would improve the therapeutic effects for treating the same, and/or would introduce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose, idea of combining them flows logically from their having been individually taught in prior art. See In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

Further, the teachings of Vite et al. that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment, and the combination cancer chemotherapy drug regimens in Merck Index, have clearly provided the motivation for the combination claimed herein.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC

SHENGJUN WANG
PRIMARY EXAMINER